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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SITTON, JEHANNE SOUAYA	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

	Application No.	Applicant(s)	
Office Action Summary	10/716,005	UHL ET AL.	
	Examiner	**Art Unit**	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 5/29/2007.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 37,45-63,69-74,78 and 79 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 37,45-63,69-74,78 and 79 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08). Paper No(s)/Mail Date 5-2007.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/29/2007 has been entered.

2. Currently, claims 37, 45-63, 69-74, and 78-79 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are newly applied, necessitated by the amendment. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is Non- FINAL.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

4. Claims 72 and 73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter Rejection.

With regard to claims 72 and 73, which depend from claim 63, although the specification provides support for upper length limitations of 30 nucleotides for primers and probes, claims 72 and 73 require that the probe comprise a nucleic acid sequence that permits secondary structure formation. The only secondary structure formation taught by the specification is directed to hairpin probes. However, the probe of SEQ ID NOS 3 is already 25 nucleotides long. With the upper length limit, the hairpin stem would only comprise 2 base pairs, whereas Tyagi teaches that hairpin stems should be at least 3 base pairs. The specification does not teach or suggest hairpin probes that comprise the indicated SEQ ID NOS and are only 30 nucleotides long.

Accordingly, the newly added claims appear to have introduced new matter into the claimed invention.

Claim Rejections - 35 USC § 103

5. Claims 37 and 45-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Telford (Telford et al; WO 02/34771; May 2002) in view of Bellin (Bellin et al; Journal of Clinical Microbiology, January 2001, vol. 39, pages 370-374) and further in view of Wittwer I.

Telford teaches that GBS is known to cause serious neonatal infections. Telford teaches nucleic acids from streptococcus group B (GBS) specifically *S. agalactiae*, including SEQ ID NO: 4465 which is the nucleic acid sequence encoding phosphoenolpyruvate phosphotransferase (ptsI). The specification does not define or provide any guidance as to the limitations of "pts", therefore the term has been given it's broadest reasonable interpretation to encompass ptsI. Telford teaches to make primers and probes using nucleic acids of GBS (see claims 12 and 19-20 of Telford) to detect Streptococcus in a biological sample (see claims 23 and 24 of Telford, also

page 6, lines 8-16). Telford does not teach the detection of GBS in a biological sample using LightCycler™ PCR. However, Bellin teaches a method of successfully detecting E. coli in a biological sample using LightCycler™ PCR. With regard to claim 37, Bellin teaches a method for the multiplex real time (claim 57) PCR detection of Enterohemorrhagic (EHEC) E. coli using a primer pair and two fluorescent hybridization probes to detect the stx1 and stx2 genes (see Table 3). Bellin teaches constructing primers and probes from a known sequence and that FRET hybridization probes were marked with LightCycler™ Red 705 and LightCycler™ Red 640 as acceptor dyes (see page 370, col. 2 "PCR primers and Probes) and fluorescein as the donor (table 3, instant claim 53). The method of Bellin involves continuously monitoring fluorescence and PCR amplification step (45 cycles: instant claims 45), wherein the biological sample is excited at a wavelength absorbed by a donor fluorescent moiety and measuring the wavelength emitted by the acceptor fluorescent moiety (see page 370, para bridging cols 1 and 2; instant claim 54) thereby quantitating the FRET (instant claim 55). Bellin further teaches determining the melting temperature (claim 58) between the stx1 and stx 2 probes wherein the melting temperature confirms the presence or absence of the Shiga toxin or Shiga toxin like producing organism (see figs 1 and 2). Bellin teaches probes which hybridize within no more than 1 nucleotide (instant claims 51 and 52) of each other (table 3), wherein one probe is labeled with a donor fluorescent moiety and the other probe is labeled with an acceptor fluorescent moiety.

Bellin teaches that the method allows for rapid identification of bacteria and complete analysis of up to 32 samples in only 45 minutes.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at time the invention was made to detect GBS using primers and probes to detect ptsI nucleic acids

in a biological sample because Telford teaches that GBS causes serious neonatal infections and teaches to use nucleic acids from GBS, including ptsI to detect bacteria in a sample. It would have further been prima facie obvious to the ordinary artisan at the time the invention was made to modify the identification method of Telford to include construction of primers and probes and the FRET detection methods as taught by Bellin for the purpose of providing a rapid method of detecting GBS in a biological sample. The ordinary artisan would have been motivated to modify the method of Telford with the detection methods of Bellin because Bellin teaches that the use of LightCycler™ PCR allows for rapid identification of bacteria and complete analysis of up to 32 samples in only 45 minutes.

With regard to claims 48-49, Bellin teaches that the cycling step was performed on an EHEC strain (EDL933) already known from a previous study (control sample) to carry stx1 and stx2. With regard to claim 50, Bellin teaches multiplexing stx1 primers and stx2 probes and stx2 primers and stx2 probes were multiplexed in the same assay (see page 372, col. 1), and that the stx double producer EDL933 showed amplification product corresponding to stx1 and stx2 (control amplification product). Therefore, it would have further been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include control sequences, including ptsI sequences from other strains of *S.agalactiae*, as well as other non ptsI nucleic acids to confirm that the primers and probes correctly identified GBS in a sample.

Telford and Bellin do not specifically teach the method wherein the detecting step is performed after each cycling step or wherein the presence of FRET within 40 or 30 cycles is indicative of GBS. However Wittwer I teaches a general method for detecting targets using primer pairs and adjacent FRET probes, wherein the detecting step is performed after each

cycling step (see col 6, lines 33-35, col 16, lines 7-10; instant claim 56). Further, Wittwer I teaches target detection after 30 and 26 cycles (col. 19 lines 14-16 and col. 20, lines 30-35; instant claims 46 and 47). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Telford and Bellin by detecting FRET after each cycling step for the purpose of detecting GBS as rapidly as possible. The ordinary artisan would have been motivated to improve the method of Telford and Bellin because Wittwer I teaches the successful identification of targets in as few as 30 and 26 cycles.

Telford and Bellin do not teach primers and probes *comprising* SEQ ID NOS 1-4, which are no longer than 30 nucleotides in length, however, Wittwer I teaches generally how to design probes for the method (col. 11, line 50-col. 12, line 39). Wittwer I also teaches that the primers are preferably 15-30 nucleotides long and that the probes can be 15-50 nucleotides long (see col. 11, lines 41-59) and exemplifies probes that are 30 nucleotides (SEQ ID NO: 6 of Wittwer I). Additionally, the primers and probes taught by Bellin are no longer than 30 nucleotides in length (see table 3).

In performing the method of Telford in view of Bellin , the ordinary artisan would be motivated to construct primers and probes as taught by Bellin for detection of GBS sequences as taught by Telford. With regard to claim 37, instantly claimed SEQ ID NOS 1-4 are found within SEQ ID NO: 4465 of Telford as follows: SEQ ID NO: 1 is identical to positions 177-199 of SEQ ID NO: 4465, SEQ ID NO: 2 is the reverse complement of positions 357-377 of SEQ ID NO: 4465, SEQ ID NO: 3 is identical to positions 265-289 of SEQ ID NO: 4465, and SEQ ID NO: 4 is identical to positions 292-311 of SEQ ID NO: 4465. Designing primers and probes to known

sequences taught in the art is routine experimentation. The prior art teaches the parameters and objectives involved in the selection of oligonucleotides that function as probes and primers, see Wittwer I. Moreover there are many internet web sites that provide free downloadable software to aid in the selection of primers drawn from genetic data recorded in a spreadsheet. The prior art is replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to design primers and probes. As discussed above, the ordinary artisan would be motivated to have designed and tested primers and probes that function to detect GBS as taught by Telford, including the instantly claimed nucleic acid sequences comprising SEQ ID NOS 1-4, as well as primers and probes which comprise one of SEQ ID NOS 1-4, which is no longer than 30 nucleotides in length. These sequences are obvious over the teachings of Telford and Bellin in view of Wittwer I.

It is noted that the specification teaches a specific assay using a primer pair consisting of SEQ ID NOS 1-2, with probes consisting of SEQ ID NOS 3 and 4, respectively, did not cross react with other non GBS bacteria, which is unexpected over the teaches of Telford and Bellin in view of Wittwer. The claims, however, are not limited to these SEQ ID NOS due to the recitation of "comprising" as well as the upper length limitation, nor are they limited to the combination of primers and probes taught in the specification.

6. Claims 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Telford in view of Bellin, further in view of Wittwer I, as applied to claims 37 and 45-58 above, and further in view of Hartley (US Patent 5,035,996; 7/30/1991).

The teachings of Telford in view of Bellin and further in view of Wittwer I are set forth above.

Telford, Bellin and Wittwer I do not teach the method comprising preventing amplification of a contaminant nucleic acid by performing amplification in the presence of uracil, and treating the sample with uracil-DNA glycosylase prior to amplification, however Hartley teaches preventing amplification of contaminants by treating samples with uracil DNA glycosylase prior to amplification, and also performing amplification in the presence of uracil. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Telford, Bellin, and Wittwer I by preventing amplification of contaminating nucleic acids with the method of preventing amplification of contaminants taught by Hartley for the purpose of making the method of Telford, Bellin, and Wittwer I more accurate.

7. Claim 62 is rejected under 35 U.S.C. 103(a) as being unpatentable over Telford in view of Bellin, further in view of Wittwer I as applied to claims 37 and 45-58 above, and further in view of Bergeron (Bergeron et al; New England Journal of Medicine, 2000, vol. 343, pages 175-179).

The teachings of Telford in view of Bellin, and further in view of Wittwer I, are set forth above.

Telford, Bellin and Wittwer I do not teach a method of nucleic acid based GBS identification in a biological sample wherein the sample is an anal/and or vaginal swab. However, Bergeron teaches studying the efficacy of PCR assays for routine screening of pregnant women for GBS at the time of delivery. Bergeron teaches obtaining anal, vaginal, and

combined anal/vaginal specimens and successfully detecting GBS (see abstract). Bergeron teaches that the sensitivity of the PCR results was 97%. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of PCR based detection of GBS of Telford, Bellin, and Wittwer I to include anal and/or vaginal sample specimens as taught by Bergeron. The ordinary artisan would have been motivated to use anal and/or vaginal specimens because Bergeron teaches that such specimens allow for the sensitivity detection of GBS in pregnant women at the time of delivery with a negative predictive value of 98.8%.

8. Claim 74 is rejected under 35 USC 103(a) as being unpatentable over Telford in view of Bellin and Buck (Buck et al Biotechniques (1999) 27(3):528-536).

Telford teaches that GBS is known to cause serious neonatal infections. Telford teaches nucleic acids from streptococcus group B (GBS) specifically *S. agalactiae*, including SEQ ID NO: 4465 which is the nucleic acid sequence encoding phosphoenolpyruvate phosphotransferase (ptsI). The specification does not define or provide any guidance as to the limitations of "pts", therefore the term has been given it's broadest reasonable interpretation to encompass ptsI. Telford teaches to make primers using nucleic acids of GBS (see claims 12 and 19-20 of Telford) to detect Streptococcus in a biological sample (see claims 23 and 24 of Telford, also page 6, lines 8-16). Telford does not teach the detection of GBS in a biological sample using LightCycler™ PCR. However, Bellin teaches a method of successfully detecting E. coli in a biological sample using LightCycler™ PCR. Bellin teaches a real time single PCR assay for detecting EHEC using a primer pair to detect stx1 and stx2 wherein the amplification product is contacted with SYBR

Green I, a double stranded nucleic acid binding dye (see page 370, col. 1, last para; and page 372, col. 1 "PCR optimization and sensitivity"). The method of Bellin involves continuously monitoring fluorescence and PCR amplification step wherein the biological sample is excited at a wavelength absorbed by a donor fluorescent moiety and measuring the wavelength emitted by the acceptor fluorescent moiety thereby quantitating the FRET. Bellin teaches that the method allows for rapid identification of bacteria and complete analysis of up to 32 samples in only 45 minutes.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at time the invention was made to detect GBS using primers and a double stranded DNA binding dye to detect ptsI nucleic acids in a biological sample because Telford teaches that GBS causes serious neonatal infections and teaches to use nucleic acids from GBS, including ptsI to detect bacteria in a sample. It would have further been prima facie obvious to the ordinary artisan at the time the invention was made to modify the identification method of Telford to include construction of primers and detection of double stranded DNA using a double stranded DNA binding dye as taught by Bellin for the purpose of providing a rapid method of detecting GBS in a biological sample. The ordinary artisan would have been motivated to modify the method of Telford with the detection methods of Bellin because Bellin teaches that the use of LightCycler™ PCR allows for rapid identification of bacteria and complete analysis of up to 32 samples in only 45 minutes.

In performing the method of Telford in view of Bellin, the ordinary artisan would be motivated to construct primers from the sequence taught by Telford. With regard to claim 74, Telford and Bellin do not teach primers comprising a sequence of SEQ ID NO: 1 or 2 which are

no more than 30 nucleotides in length, however instantly claimed SEQ ID NOS 1-2 are found within SEQ ID NO: 4465 of Telford as follows: SEQ ID NO: 1 is identical to positions 177-199 of SEQ ID NO: 4465, SEQ ID NO: 2 is the reverse complement of positions 357-377 of SEQ ID NO: 4465. Further, Buck expressly provides evidence of the equivalence of primers in amplifying sequences and exemplifies the use of primers which are less than 30 nucleotides long. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success in hybridizing to and functioning as a primer to the target it is designed for.

Therefore, it would have been prima facie obvious to the ordinary artisan at the time the invention was made to construct primers for performing the method of Telford and Bellin,

including primers comprising SEQ ID NOS 1 and 2, which are no more than 30 nucleotides in length. Designing primers and probes to known sequences taught in the art is routine experimentation. The prior art teaches the parameters and objectives involved in the selection of oligonucleotides that function as primers. Moreover there are many internet web sites that provide free downloadable software to aid in the selection of primers drawn from genetic data recorded in a spreadsheet. The prior art is replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to design primers and probes. As discussed above, the ordinary artisan would be motivated to have designed and tested primers and probes that function to detect GBS as taught by Telford, including the instantly claimed nucleic acid sequences comprising SEQ ID NOS 1-2, which are no more than 30 nucleotides in length. These sequences are obvious over the teachings of Telford in view of Bellin and Buck.

9. Claims 78-79 are rejected under 35 USC 103(a) as being unpatentable over Telford in view of Bellin and Buck, as applied to claims 74 above, and further in view of Wittwer II (Wittwer et al; US Patent 6,174,670; 1/16/2001).

The teachings of Telford in view of Bellin and Buck are set forth above.

Telford, Bellin and Buck do not teach determining the melting temperature between the amplification product and the double stranded nucleic acid binding dye, however Wittwer II teaches determining the melting temperature between the amplification product and double stranded binding dye for the purpose of correcting for nonspecific amplification, improving sensitivity of PCR, monitoring product hybridization, and product quantification by reannealing kinetics (col. 3, lines 30-50). Wittwer II specifically teaches a method of real time monitoring of

a PCR reaction by amplifying the target by PCR in the presence of SYBR Green I, exciting the biological sample with light and detecting the emission, and monitoring the temperature dependent fluorescence from SYBR Green I (see col. 7, lines 13-31). Further, Wittwer II specifically teaches analysis using the DNA binding dye ethidium bromide (see col. 11, lines 10-38; col. 22,lines 54-66). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of detection of GBS of Telford, Bellin and Buck to include the step of determining the melting temperature between the amplification product and double stranded binding dye, for the purpose of correcting for nonspecific amplification, improving sensitivity of PCR, monitoring product hybridization, and product quantification by reannealing kinetics, as taught by Wittwer II.

10. Claims 63, 72 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Telford in view of Belanger (Belanger et al; Journal of Clinical Microbiology, vol. 40, pages 1436-1440, April 2002) and further in view of Buck and Tyagi (Tyagi et al; US Patent 5,925,517).

Telford teaches that GBS is known to cause serious neonatal infections. Telford teaches nucleic acids from streptococcus group B (GBS) specifically S. *agalactiae*, including SEQ ID NO: 4465 which is the nucleic acid sequence encoding phosphoenolpyruvate phosphotransferase (ptsI). Telford teaches to make primers and probes using nucleic acids of GBS for (see claims 12 and 19-20 of Telford) to detect Streptococcus in a biological sample (see claims 23 and 24 of Telford, also page 6, lines 8-16). Telford does not teach the detection of GBS in a biological

sample using PCR followed by hybridization with a molecular beacon probe labeled with a donor and corresponding acceptor fluorescent moiety.

However, Belanger teaches a method for the detection of shiga toxin producing E. coli by detection of the stx1 and stx2 genes (Shiga like toxin producing organism). The method of Belanger uses a pair of primers to amplify either stx1 or stx2 (amplification step) and a molecular beacon probe (hybridizing step) to detect the presence of the E. coli strains which do contain the stx1 or stx2 genes and distinguish them from strains that do not (see page 1438, col. 1), using the presence or absence of fluorescence for detection. It is noted that molecular beacon probes comprise a single stranded sequence which permits secondary structure formation (hairpin) wherein the secondary structure results in spatial proximity between the donor and acceptor fluorescent moiety. Further, the acceptor moiety in a molecular beacon probe is a quencher. Belanger teaches that the method is rapid, simple and sensitive and allowed detection of bacteria in a sample where the bacteria were not detected by conventional culture methods (see abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detect GBS using primers and probes to detect ptsI nucleic acids in a biological sample because Telford teaches that GBS causes serious neonatal infections and teaches to use nucleic acids from GBS, including ptsI to detect bacteria in a sample. It would have further been prima facie obvious to the ordinary artisan at the time the invention was made to modify the identification method of Telford to include construction of primers and a molecular beacon probe and the fluorescence based PCR methods as taught by Belanger for the purpose of providing a rapid method of detecting GBS in a biological sample. The ordinary artisan would

have been motivated to modify the method of Telford with the detection methods of Belanger because Belanger teaches that the use of a molecular beacon probe in a fluorescence based PCR detection method allows for rapid, simple and sensitive identification of bacteria.

Telford and Belanger do not teach primers and probes comprising SEQ ID NOS: 1-4, which are no longer than 30 nucleotides in length, however in performing the method of Telford and Belanger, the ordinary artisan would be motivated to construct primers and probes for use in the method. Tyagi teaches the use of hairpin probes for target detection and teaches that the target complementary portion of the probe can be 15-35 nucleotides long, while the arm (self complementary stem) length can be from 3-25 nucleotides in length (see col. 12, lines 47-55). Further, Buck expressly provides evidence of the equivalence of primers in amplifying sequences and exemplifies the use of primers less than 30 nucleotides long. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however

different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success in hybridizing to and functioning as a primer to the target it is designed for.

Therefore it would have been prima facie obvious to the one of ordinary skill in the art at the time the invention was made to construct a number of primers and probes for use in the method of Telford in view of Belanger. With regard to claim 63, instantly claimed SEQ ID NOS 1-2 and 4 are found within SEQ ID NO: 4465 of Telford as follows: SEQ ID NO: 1 is identical to positions 177-199 of SEQ ID NO: 4465, SEQ ID NO: 2 is the reverse complement of positions 357-377 of SEQ ID NO: 4465, and SEQ ID NO: 4 is identical to positions 292-311 of SEQ ID NO: 4465. Designing primers and probes to known sequences taught in the art is routine experimentation. The prior art teaches the parameters and objectives involved in the selection of oligonucleotides that function as probes and primers, see Tyagi and Buck. Moreover there are many internet web sites that provide free downloadable software to aid in the selection of primers drawn from genetic data recorded in a spreadsheet. The prior art is replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to design primers and probes. As discussed above, the ordinary artisan would be motivated to have designed and tested primers and probes that function to detect GBS as taught by Telford in view of Belanger, including the instantly claimed nucleic acid sequences comprising SEQ ID NOS 1-2 and 4, which are not longer than 30 nucleotides. These sequences are considered obvious over the teachings of Telford and Bellin in view of Tyagi and Buck.

11. Claims 63 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Telford in view of Pfeffer (Pfeffer et al; WO 98/48046) and Buck.

Telford teaches that GBS is known to cause serious neonatal infections. Telford teaches nucleic acids from streptococcus group B (GBS) specifically S. *agalactiae*, including SEQ ID NO: 4465 which is the nucleic acid sequence encoding phosphoenolpyruvate phosphotransferase (ptsI). Telford teaches to make primers and probes using nucleic acids of GBS for (see claims 12 and 19-20 of Telford) to detect Streptococcus in a biological sample (see claims 23 and 24 of Telford, also page 6, lines 8-16). Telford does not teach the detection of GBS in a biological sample using a PCR assay that employs the 5'-3' exonuclease activity of Taq polymerase.

However, Pfeffer teaches a method of detecting enterohemorrhagic E. coli by using a PCR assay that employs the 5'-3' exonuclease activity of Taq polymerase (TAQMAN™) together with a flourogenic probe (see page 4, lines 18-23; page 5, lines 24-26; page 9, lines 5-10). Pfeffer teaches that the method utilizes primers (page 8, lines 21-30) and a probe (page 10, lines 15-24) for the detection of the SltI and SltII wherein detection of the presence of fluorescence resonance energy transfer is indicative of the presence of the enterohemorrhagic E. coli (see also, page 25-26 and tables 2- 4). Pfeffer exemplifies the use of probes that are 30 nucleotides long. Pfeffer teaches that the use of the TAQMAN™ assay allows for the specific, rapid and high throughput detection of specific bacteria.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detect GBS using primers and a probes to detect ptsI nucleic acids in a biological sample because Telford teaches that GBS causes serious neonatal infections and teaches to use nucleic acids from GBS, including ptsI to detect bacteria in a sample. It

would have further been prima facie obvious to the ordinary artisan at the time the invention was made to modify the identification method of Telford to include construction of primers and a flourescent probe as taught by Pfeffer for the purpose of providing a rapid method of detecting GBS in a biological sample. The ordinary artisan would have been motivated to modify the method of Telford with the detection methods of Pfeffer because Pfeffer teaches that the use of a fluorescently labeled probe in a TAQMAN™ detection method allows for rapid, simple and sensitive identification of bacteria.

Telford and Pfeffer do not teach primers and probes comprising SEQ ID NOS: 1-4, which are not longer than 30 nucleotides, however in performing the method of Telford and Pfeffer, the ordinary artisan would be motivated to construct primers and probes for use in the method. Pfeffer teaches the construction of primer and probes for use in the method and Buck expressly provides evidence of the equivalence of primers in amplifying sequences and exemplifies the use of primers less than 30 nucleotides. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)."

Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success in hybridizing to and functioning as a primer to the target it is designed for.

Therefore it would have been prima facie obvious to the one of ordinary skill in the art at the time the invention was made to construct a number of primers and probes for use in the method of Telford in view of Pfeffer. With regard to claim 63, instantly claimed SEQ ID NOS 1-4 are found within SEQ ID NO: 4465 of Telford as follows: SEQ ID NO: 1 is identical to positions 177-199 of SEQ ID NO: 4465, SEQ ID NO: 2 is the reverse complement of positions 357-377 of SEQ ID NO: 4465, SEQ ID NO: 3 is identical to positions 265-289 of SEQ ID NO: 4465, and SEQ ID NO: 4 is identical to positions 292-311 of SEQ ID NO: 4465. Designing primers and probes to known sequences taught in the art is routine experimentation. The prior art teaches the parameters and objectives involved in the selection of oligonucleotides that function as probes and primers, see Pfeffer and Buck. Moreover there are many internet web sites that provide free downloadable software to aid in the selection of primers drawn from genetic data recorded in a spreadsheet. The prior art is replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to design primers and probes. As discussed above, the ordinary artisan would be motivated to have designed and tested primers and probes that function to detect GBS as taught by Telford in view of Pfeffer, including the instantly claimed nucleic acid sequences comprising SEQ ID NOS 1-4, which are not longer than

30 nucleotides. These sequences are considered obvious over the teachings of Telford in view of Pfeffer and Buck.

12. Claims 70-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Telford in view of Pfeffer and Buck as applied to claims 63 and 69 above, and further in view of Livak et al (US Patent 5,538,848 1995).

The teachings of Telford, Pfeffer and Buck are set forth above.

Telford, Pfeffer, and Buck do not teach a method wherein the donor and acceptor moieties are within no more than 5 nucleotides of each other on the probe, however, Livak teaches a method of detecting hybridization of flourogenic probe in a 5' nucleic assay, and teaches that traditionally, the donor and quencher are separated by about 6-16 nucleotides of each other on the probe (see col. 2, lines 45-50). The recitation of "about 6" has been interpreted to encompass 5 nucleotides apart. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Telford, Pfeffer and Buck to use probes wherein the donor and quencher are within no more than 5 nucleotides of each other because Livak teaches that such orientation provides sufficient spacing for the purposes of detecting hybridization of the probe in the 5'nuclease (Taqman) assay. The ordinary artisan would have been motivated to modify the probe used by Telford, Pfeffer, and Buck as taught by Livak for the purpose of making the method of Telford, Pfeffer, and Buck more versatile to perform.

13. Claims 37, 45-61, 63, 69-74 and 78-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Telford in view of Uhl (Uhl et al; US patent 6,593,093).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). *This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).*

Telford teaches that GBS is known to cause serious neonatal infections. Telford teaches nucleic acids from streptococcus group B (GBS) specifically *S. agalactiae*, including SEQ ID NO: 4465 which is the nucleic acid sequence encoding phosphoenolpyruvate phosphotransferase (ptsI). Telford teaches to make primers and probes using nucleic acids of GBS (see claims 12 and 19-20 of Telford) to detect Streptococcus in a biological sample (see claims 23 and 24 of Telford, also page 6, lines 8-16). Telford does not teach the detection of GBS in a biological sample using LightCycler™ PCR, molecular beacon probes, or the TAQMAN™ assay. However, Uhl teaches a method of successfully detecting Group A Streptococcus (GAS) in a biological sample by using primers and probes to pstI nucleic acids using various methods

including LightCycler™ PCR, molecular beacon probes, or the TAQMAN™ assay (see claims 1-21 and 27-35 of Uhl). Further Uhl teaches that primers and probes are 8-50 nucleotides, including up to 30 nucleotides in length (see col. 5). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detect GBS using primers and a probes to detect ptsI nucleic acids in a biological sample because Telford teaches that GBS causes serious neonatal infections and teaches to use nucleic acids from GBS, including ptsI to detect bacteria in a sample. It would have further been prima facie obvious to the ordinary artisan at the time the invention was made to modify the identification method of Telford to include construction of primers and probes for use in LightCycler™ PCR, molecular beacon probe assays, and the TAQMAN™ assay as taught by Uhl for the purpose of providing a method of detecting GBS in a biological sample. The ordinary artisan would have been motivated to modify the method of Telford with the detection methods of Uhl because Uhl teaches that the use of LightCycler™ PCR, molecular beacon probe assays, and the TAQMAN™ allows for sensitive identification of streptococcus bacteria.

Additionally, instantly claimed SEQ ID NO: 2 is identical to SEQ ID NO: 2 of Uhl. Telford and Uhl do not teach primers and probes *comprising* SEQ ID NOS 1, and 3-4, which are not longer than 30 nucleotides, however, in performing the method of Telford in view of Uhl, the ordinary artisan would be motivated to construct primers and probes as taught by Uhl for detection of GBS sequences as taught by Telford. Instantly claimed SEQ ID NOS 1-4 are found within SEQ ID NO: 4465 of Telford as follows: SEQ ID NO: 1 is identical to positions 177-199 of SEQ ID NO: 4465, SEQ ID NO: 2 is the reverse complement of positions 357-377 of SEQ ID NO: 4465, SEQ ID NO: 3 is identical to positions 265-289 of SEQ ID NO: 4465, and SEQ ID

NO: 4 is identical to positions 292-311 of SEQ ID NO: 4465. Designing primers and probes to known sequences taught in the art is routine experimentation. The prior art teaches the parameters and objectives involved in the selection of oligonucleotides that function as probes and primers, see Uhl. Moreover there are many internet web sites that provide free downloadable software to aid in the selection of primers drawn from genetic data recorded in a spreadsheet. The prior art is replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to design primers and probes. As discussed above, the ordinary artisan would be motivated to have designed and tested primers and probes that function to detect GBS as taught by Telford, including the instantly claimed nucleic acid sequences comprising SEQ ID NOS 1-4 which are no longer than 30 nucleotides.

14. Claim 62 is rejected under 35 U.S.C. 103(a) as being unpatentable over Telford in view of Uhl as applied to claims 37, 45-61 above, and further in view of Bergeron (Bergeron et al; New England Journal of Medicine, 2000, vol. 343, pages 175-179).

The teachings of Telford in view of Uhl are set forth above.

Telford and Uhl do not teach a method of nucleic acid based GBS identification in a biological sample wherein the sample is an anal/and or vaginal swab. However, Bergeron teaches studying the efficacy of PCR assays for routine screening of pregnant women for GBS at the time of delivery. Bergeron teaches obtaining anal, vaginal, and combined anal/vaginal specimens and successfully detecting GBS (see abstract). Bergeron teaches that the sensitivity of the PCR results was 97%. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of PCR based detection

of GBS of Telford and Uhl, to include anal and/or vaginal sample specimens as taught by Bergeron. The ordinary artisan would have been motivated to use anal and/or vaginal specimens because Bergeron teaches that such specimens allow for the sensitivity detection of GBS in pregnant women at the time of delivery with a negative predictive value of 98.8%.

Response to Arguments

15. The response filed 5/29/2007 traverses the rejection and asserts that the claims have been amended to particularly claim a combination of 2 or 4 oligonucleotides. This argument has been thoroughly reviewed but was not found persuasive. In the claims, the term "or" is used repeatedly, such that many claims only encompass 2 oligonucleotides SEQ ID NOS (claim 37) as well as only 1 oligo SEQ ID NO (claim 74). Additionally, given that the claims list that the oligos can be up to 30 nucleotides long, the claims actually encompass a larger genus of possible probes and primers than the actual SEQ ID NOS listed. The response asserts that Buck does not provide a reasonable expectation of success because Buck did not use GBS nucleic acid, and the primers used by Buck were sequencing primers and teaches sequencing using a single oligonucleotide. This argument has been thoroughly reviewed but was not found persuasive. The teachings of Buck, regardless of whether the primers are used singly or in combination, show that many different possible oligonucleotides can be made to a known sequence to function as a primer. The response provides no reasoning as to why a PCR primer pair would have a different expectation of success especially given that the art was replete with guidance on how to pick oligonucleotides to known sequences to function in hybridization as primers or probes (see Buck, Wittwer I, Wittwer II, Tyagi, Pfeffer, Bellinger, Bellin, as well as applicant's own cited

art: Lowe, Elnifro, Abd-Elsalam, etc). The response further asserts that primer design for PCR amplification and probe design for real time PCR amplification frequently is not predictable and cites the guidelines published by the Chicago Cancer Research Center DNA Sequencing facility. As no reference was provided, the examiner is unable to address this assertion. The response cites Csordas et al (2004, Lett. App. Microbiol., 39:187-193) as stating that "primers originally designed for end-point PCR did not have adequate specificity or sensitivity compared to those for real time PCR", Elnifro (2000, Clin Microbiol Rev, 13:559-570) as stating "empirical testing and a trial and error approach may have to be used..."; Tichopad et al (2004, Mol. Cell Probes, 18:45-50) as stating "unknown tissue specific factors can influence amplification kinetics..."; Abd-Elsalam (2003, African J. Biotech, 2:91-95) as stating "the most critical parameter for successful PCR is the design of primers"; and Ballard et al (2005, Antimicrob. Agents, Chemotherapy, 49:77-81). The references were thoroughly reviewed but were not found persuasive to overcome the rejection. Csordas and Ballard do not appear to teach that the primers did not work in amplification, but rather that they were not as specific or sensitive as other primers. Elnifro and Abd-Elsalam represent teachings that illustrate the level of skill in the art at the time the invention was filed, and teachings that were available to the ordinary artisan. Abd-Elsalam specifically lists parameters [page 94], as well as web sites [page 93] that illustrate the level of skill in the art at the time the invention was filed. They do not illustrate that primers and probes cannot be made to amplify and hybridize to a known target. Tichopad also illustrates that every primer used could amplify the target sequence. As also noted in each rejection, Buck specifically exemplifies the equivalence of oligonucleotides in functioning as primers to a known target.

The response then asserts with regard to *In re Jones* (Fed. Cir 1992) and *In re Bell* (Fed Cir 1993), that based on current case law, each of the claimed primer and probe sequences are not obvious over the cited references. These arguments have been thoroughly reviewed but are unpersuasive. Firstly, although the claims recite specific SEQ ID NOs, they are not directed to specific primers or probes as the claims continue to recite "comprising", albeit with an upper length limitation, and which encompasses a genus of possible sequences which comprise the indicated SEQ ID NOS. Secondly, the instant rejection did not set forth that it would be obvious to obtain the claimed SEQ ID NO: from protein sequences, but from alignments of specific nucleic acid sequences taught in the art. At the time the invention was filed, the prior art was replete with examples of how to construct probes and primers for use with the claimed methodologies. The prior art specifically exemplify that constructing primers and probes to detect known targets is in fact predictable, using the methods claimed. No case law is needed to establish this scientific fact which is specifically exemplified numerous times in the cited references.

The response cites *In re Deuel* (Fed. Cir 1995) and asserts "Specifically, *In re Deuel* states that methods of isolating and making specific DNA molecules are not obvious over the prior art that does no disclose the specific DNA molecules". This argument has been thoroughly reviewed and was found persuasive to overcome the rejections. The claimed SEQ ID NOS are identical to regions of GBS sequences already known in the art at the time the invention was made. In contrast to the instant claims, the issue in *Deuel* was that the nucleic acid sequence was not taught in the prior art.

With regard to arguments regarding the non-obviousness of species over the prior art teaching of a genus have been thoroughly reviewed but was not found persuasive. Given the teachings in the prior art of specifically making oligonucleotides to detect a known target nucleic acid, the prior art provides ample motivation to make a number of primers and probe which would function to detect GBS. The genus is not so large as to encompass anywhere on the GBS genome, but is rather directed to smaller sequences which the prior art specifically teaches how to target and provides motivation to do so.

The response further asserts that the current rejections that use specific primer or probe sequences are not constituent with the standard for obviousness, citing the recent Supreme Court decision KSR Int'l Co. v. Teleflex Inc., 550 U.S. _ (2007) "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness". The response asserts that applicants believe the examiner is making conclusory statements regarding the efficacy of "all primers" based on Buck et al. when, in fact Applicants have provided evidence in the form of more recently published references that discuss and provide experimental evidence demonstrating the unpredictability of primer and probe design. These arguments have been thoroughly reviewed but were not found persuasive. The examiner has not made conclusory statements, but has actually used reasoning and rational found in the prior art itself. The teachings of Buck have already been discussed above. Buck exemplifies that current technology allows the selection of a large number of possible oligos from known sequences for use as primers. Further the cited art, both in the rejections as well as applicant's arguments, provides ample criteria on how to design sequences as probes and primers for use in the claimed

methods. Additionally, in many cases, the art cited by the response actually shows the state of the art, known and readily available to the ordinary artisan regarding the use of already known sequences to design probes and primers. Particularly, Elnifro and Abd-Elsalam represent teachings that illustrate the level of skill in the art at the time the invention was filed, and teachings that were available to the ordinary artisan. Abd-Elsalam specifically lists parameters [page 94], as well as web sites [page 93] that illustrate the level of skill in the art at the time the invention was filed on how to design oligonucleotides for detection. They do not illustrate that primers and probes cannot be made to amplify and hybridize to a known target.

With regard to the citation of the recent Supreme Court decision and statement "[t]he fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that [the claim] was not obvious to those skilled in the art", it is noted that none of the claims are directed to the particular combination of specific probes and primers used in the example in the specification. In fact, the office action has specifically set forth that the combination of a primer pair consisting of SEQ ID NOS 1-2, and the probe pair consisting of SEQ ID NOS 3 and 4, in the method of claim 37, is not obvious over the teachings of Telford and Bellin in view of Wittwer I (see section 5 above) given the unexpected results set forth in the specification. The examiner disagrees that the rejections are not consistent with the decision in KSR. The Supreme Court stated: "When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, in either the same field or a different one. If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability." In the instant case, as is exemplified by the numerous teachings in the cited prior art, designing probes and primers to target known nucleic acid sequences using different methodologies (molecular

beacon assay, Lightcycler™ PCR, etc) including those claimed, was routine to the ordinary artisan. The technology to design probes and primers using already known sequence targets, and designing primers and probes based on different parameters needed for each different methodology, was already taught. In this situation, designing probes and primers, including the claimed sequences, was predictable given the ample teachings in the cited art on how to do so, as well as the motivation as exemplified by the teachings of the prior art on why the ordinary artisan would be motivated to do so. The rejections are therefore maintained.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton
Primary Examiner
Art Unit 1634

7/30/07